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Prognostic impact of beta-blocker compared to combined amiodarone therapy secondary to ventricular tachyarrhythmias☆

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ABSTRACT

Objective: The study sought to assess the prognostic impact of treatment with beta-blocker (BB) compared to combined BB plus amiodarone (BB-AMIO) on long-term survival in patients surviving ventricular tachyarrhythmias on admission.
Background: Data regarding the prognostic outcome of patients presenting with ventricular tachyarrhythmias treated with BB and BB-AMIO is limited.
Methods: A large retrospective registry was used including consecutive patients surviving index episodes of ventricular tachyarrhythmias from 2002 to 2016. Patients treated with BB were compared to patients with BB-AMIO. The primary prognostic endpoint was long-term all-cause death at 3 years. Kaplan-Meier, multivariable Cox regression and propensity score matching analyses were applied.
Results: A total of 1354 patients was included, 85% treated with BB, 15% with BB-AMIO. Within the unmatched real-life cohort, uni- and multivariable Cox regression models revealed BB associated with improved long-term survival compared to BB-AMIO (univariable: HR = 0.550; $p = 0.001$, multivariable: HR = 0.712; statistical trend, $p = 0.052$). After propensity-score matching ($n = 186$ matched pairs), BB therapy was still associated with improved survival compared to BB-AMIO (mortality rate 18% versus 26%; log rank $p = 0.042$; HR = 0.634; 95% CI = 0.407–0.988; $p = 0.044$). Prognostic superiority of BB was mainly observed in patients with LVEF ≥ 35% (HR = 0.463; 95% CI = 0.215–0.997; $p = 0.049$) and in those without atrial fibrillation (non-AF) (HR = 0.415; 95% CI = 0.202–0.852; $p = 0.017$).
Conclusion: BB therapy is associated with improved secondary long-term prognosis compared to BB-AMIO in patients surviving index episodes of ventricular tachyarrhythmias.

1. Introduction

Sudden cardiac death (SCD) accounts for almost half of all cardiac deaths [1,2] and may be caused by hemodynamically unstable ventricular tachycardia (VT) degenerating into ventricular fibrillation (VF) [1–4]. Preventive strategies include implantation of cardioverter defibrillators (ICD) [4–7] and additional pharmacological treatment in order to reduce adverse cardiac remodelling, recurrent episodes of ventricular tachyarrhythmias and mortality [3].

Amiodarone (AMIO) was shown to prevent and inhibit the occurrence of arrhythmias and cardiac automacy [8,9]. As a class III antiarrhythmic drug it reveals multi-pharmacological effects, including blockage of sodium channels, calcium channels and non-competitive beta-blockage. AMIO is therefore indicated in patients suffering from supra- and ventricular tachycardia including atrial fibrillation (AF), VT and VF [10–13]. AMIO is also indicated during cardiopulmonary resuscitation (CPR) after

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ineffective external cardioversion/defibrillation of VT/VF [9,14]. According to other antiarrhythmic drugs AMIO reveals several side effects, such as hyperthyroidism, pulmonary fibrosis, hepatitis, corneal micro-deposits and QTc prolongation, as well as light-sensitive blue-grey discoloration of the skin at long-term administration [9,11,15,16]. Nevertheless, AMIO is indicated in patients with structural heart disease including heart failure. However, the potential prognostic benefit of AMIO is still under debate [15,17,18]. Typically, AMIO is prescribed in combination with beta-blockers (BB), since this combination was shown to reduce the number of adequate ICD shocks [9,19]. BB are first-line therapy in patients with VT and VF, since they may reduce ectopic beats and prevent SCD via multiple further pathways [9]. However, the benefit of combined BB-AMIO compared to BB alone is still unclear [20].

Therefore, this study evaluates the prognostic impact of BB versus BB-AMIO in patients surviving index episodes of ventricular tachyarrhythmias on long-term all-cause mortality.

2. Methods

2.1. Study patients, design and data collection

The present study included retrospectively all patients surviving at least one episode of ventricular tachyarrhythmias from 2002 until 2016 at one institution. All relevant clinical data related to the index event was documented using patients' files, daily records, documentation from diagnostic examinations and laboratory values, electrocardiograms (ECG), device recordings, and all further information derived from the electronic hospital information system.

Ventricular tachyarrhythmias comprised VT and VF, as defined by current international guidelines [21]. Sustained VT was defined by VT with a duration of ≥30 s or additional hemodynamic collapse within 30 s. Sustained VT was defined by VT with a duration of ≥30 s. VT comprised wide QRS complex (≥120 ms) at a rate > 100 beats/min [21]. Ventricular tachyarrhythmias were documented by 12-lead ECG, ECG tele-monitoring, ICD or in case of unstable course or during resuscitation by external defibrillator monitoring. Documented VF was treated by external defibrillation and in case of prolonged instability with additional intravenous anti-arrhythmic drugs during CPR. Further documented data contained baseline characteristics, prior medical history, prior medical treatment, length of index stay, detailed findings of laboratory values at baseline, data derived from all non-invasive or invasive cardiac diagnostics and device therapies. These included coronary angiography, electrophysiological examination, prior or newly implanted ICDs, pacemakers or cardiac contractility modulators (CCM), which were already implanted at index or at follow-up. Imaging modalities comprised echocardiography or cardiac magnetic resonance imaging (cMRI). The overall presence of an activated ICD summarizes the total sum of all patients with a prior implanted ICD before admission, those undergoing new ICD implantation at index stay, as well as those with ICD implantation at the complete follow-up period after index hospitalization, referring to sole transvenous ICD, subcutaneous-ICD (s-ICD) and cardiac resynchronization therapy with defibrillator function (CRT-D). Documentation period lasted from index event until 2016. Documentation of all medical data was performed by independent cardiologists at the patients' individual period of hospitalization blinded to final data analyses.

The present study is derived from an analysis of the "Registry of Malignant Arrhythmias and Sudden Cardiac Death - Influence of Diagnostics and Interventions (RACE-IT)" and represents a single-center registry including consecutive patients presenting with ventricular tachyarrhythmias and aborted cardiac arrest being acutely admitted to the University Medical Center Mannheim (UMM), Germany (clinicaltrials.gov identifier: NCT02982473) from 2002 until 2016. The registry was carried out according to the principles of the declaration of Helsinki and was approved by the medical ethics committee II of the Medical Faculty Mannheim, University of Heidelberg, Germany.

The medical centre covers a general emergency department (ED) for emergency admission of traumatic, surgical, neurological and cardiovascular conditions. Interdisciplinary consultation is an inbuilt feature of this 24/7 service, and connects to a stroke unit, four intensive care units (ICU) with extracorporeal life support and a chest pain unit (CPU) to alleviate rapid triage of patients. The cardiologic department itself includes a 24 h catheterization laboratory, an electrophysiologic laboratory, a hybrid operating room and telemetry units.

2.2. Risk stratification, inclusion and exclusion criteria

For the present study, all patients surviving index hospitalization after presenting with ventricular tachyarrhythmias between 2002 and 2016 were included as previously being described. [22]

Despite the retrospective study design, risk stratification was performed as follows: Firstly, all patients were included and analyzed according to the presence of BB or BB-AMIO at discharge from index hospitalization, as being prescribed by the intention of the physicians during clinical care (intention-to-treat). Secondly, results were re-evaluated in patients without any evidence of discontinuing pharmacological therapies only, which reflects an as-treated status.

The BB-group comprised patients with sole BB but without AMIO, the BB-AMIO-group comprised patients with BB and AMIO. All kinds of BB were allowed and individual dosages at discharge were documented. All other medical therapies apart from BB or BB-AMIO were allowed.

Indication to treat patients with BB and AMIO was based on European guidelines on heart failure and ventricular tachyarrhythmias [21,23]. Patients not surviving index hospitalization and patients discharged without BB were excluded from the present study. No further exclusion criteria were present.

2.3. Study endpoints

The primary prognostic endpoint was all-cause mortality during the follow-up period until 2016. All-cause mortality was documented using our electronic hospital information system and by directly contacting state resident registration offices ("bureau of mortality statistics") across Germany. Identification of patients was verified by place of name, surname, day of birth and registered living address. In 48 patients, no data on patients´ survival could have been retrieved, as those patients were even not reachable by telephone, and therefore these patients were excluded from final analyses (i.e. lost to follow-up).

2.4. Propensity-score matching

In randomized controlled trials (RCTs) patients with or without a specific treatment (such as BB or BB-AMIO) would have a 50% chance to be treated. Balanced measured and unmeasured baseline characteristics would then be expected. In an observational study, recruiting real-life patients, the specific treatment would not be randomized resulting in varying chances between 0% and 100% to receive it, including imbalances in baseline characteristics. Consecutively, differences of outcomes in specific treatment groups might be explained by heterogenous distribution of baseline characteristics. To reduce this selection bias, we used 1:1 propensity scores for the receipt of a specific discharge medication (i.e. BB or BB-AMIO) to assemble a matched cohort in which patients receiving and not receiving the discharge medication would be well balanced on all measured baseline characteristics.

1:1 propensity score matching was performed including the entire study cohort performing a non-parsimonious multivariable logistic regression model using patients with the specific treatment as the dependent variable [24,25]. Propensity scores were created according to the presence of the following independent variables: age, gender, atrial fibrillation, degree of left ventricular dysfunction, CPR, ST-segment myocardial infarction (STEMI), non-ST myocardial infarction (NSTEMI) and presence of an ICD on admission.

Based on the propensity score values counted by logistic regression, for each patient in the treatment group one patient in the control group with a similar propensity score value was found (accepted difference of propensity score value < 5%).

2.5. Statistical methods

Statistics were performed within the real life cohort as well as in the propensity-matched subgroup. Quantitative data are presented as mean ± standard error of mean (SEM), median and interquartile range (IQR), and ranges depending on the distribution of the data and were compared using the Student's *t*-test for normally distributed data or the Mann-Whitney *U* test for nonparametric data. Deviations from a Gaussian distribution were tested by the Kolmogorov-Smirnov test. Spearman's rank correlation for nonparametric data was used to test univariate correlations. Qualitative data are presented as absolute and relative frequencies and compared using the Chi^2 test or the Fisher's exact test, as appropriate. Univariable Kaplan-Meier survival curves were calculated. Multivariable Cox regression models were developed using the "forward selection" option, where only statistically significant variables ($p < 0.05$) were included and analyzed simultaneously. Multivariable Cox regressions were applied in within the entire unmatched cohort and stratified by subgroups (gender, VT/VF, LV dysfunction, presence of ICD (including ICDs and s-ICDs) or CRT-D, ICD implant indication, AF and ablation therapy at index). Afterwards, univariable Kaplan-Meier survival curves were applied in the propensity-matched subgroup. Hazard ratios (HR) are given together with 95% confidence intervals. Follow-up periods for evaluation of all-cause mortality were set at three years (=long-term). Patients not meeting long-term follow-up were censored. The result of a statistical test was considered significant for $p < 0.05$, and a statistical trend for $p < 0.10$. SAS, release 9.4 (SAS Institute Inc., Cary, NC, USA) and SPSS (Version 25, IBM, Armonk, New York) were used for statistics.

3. Results

3.1. Unmatched entire study cohort

In this real-life cohort of 1354 consecutive patients surviving at least one episode of ventricular tachyarrhythmias on admission at our institution, significantly more patients were treated with BB compared to BB-AMIO (85 vs. 15%; $p = 0.0001$) (Table 1, left panel).

Target dosages were reached already at discharge, including metoprolol as the most frequently administered type of BB (mean dosage 76–79 mg per day) followed by carvedilol (mean dosage 20–22 mg

Table 1
Patients' characteristics.

Characteristic	Before matching ($n = 1354$)					After matching ($n = 372$)				
	BB ($n = 1144$; 85%)		BB-AMIO ($n = 210$; 15%)		p Value	BB (n = 186;50%)		BB-AMIO (n = 186;50%)		p Value
Male gender, n (%)	832	(73)	180	(86)	**0.001**	157	(84)	159	(86)	0.772
Age, median (range)	65 (15–92)		69 (22–90)		**0.001**	65 (20–87)		69 (22–90)		**0.001**
Ventricular tachyarrhythmias, n (%)										
Ventricular tachycardia	759	(66)	158	(75)		143	(77)	138	(74)	
Ventricular fibrillation	385	(34)	52	(25)	**0.011**	43	(23)	48	(26)	0.546
Prior medical history, n (%)										
Chronic heart failure	271	(24)	94	(45)	**0.001**	85	(46)	88	(47)	0.755
Coronary artery disease	481	(42)	125	(60)	**0.001**	119	(64)	113	(61)	0.521
Chronic kidney disease	440	(39)	111	(54)	**0.001**	84	(45)	96	(53)	0.160
Liver cirrhosis	9	(0.8)	0	(0)	0.370	2	(1)	0	(0)	0.499
COPD/asthma	92	(8)	22	(11)	0.243	20	(11)	20	(11)	1.000
Cardiovascular risk factors, n (%)										
Arterial hypertension	690	(60)	145	(69)	**0.017**	128	(69)	125	(67)	0.739
Diabetes mellitus	274	(24)	75	(36)	**0.001**	47	(25)	65	(35)	**0.042**
Hyperlipidemia	385	(34)	72	(34)	0.859	79	(43)	63	(34)	0.088
Smoking	365	(32)	60	(29)	0.339	69	(37)	55	(30)	0.124
Cardiac family history	138	(12)	23	(11)	0.648	31	(17)	22	(12)	0.182
Acute comorbidities at index, n (%)										
Acute myocardial infarction	339	(30)	38	(18)	**0.001**	33	(18)	31	(17)	0.784
STEMI	139	(13)	4	(2)	**0.001**	6	(3)	3	(2)	0.502
NSTEMI	200	(18)	34	(16)	0.649	27	(15)	28	(15)	0.884
Cardiogenic shock	95	(8)	20	(9)	0.560	16	(9)	17	(9)	0.855
Atrioventricular block	33	(3)	3	(1)	0.228	6	(3)	3	(2)	0.311
Stroke	25	(2)	9	(4)	0.074	5	(3)	8	(4)	0.397
Intracranial hemorrhage	8	(0.7)	1	(1)	0.715	3	(2)	1	(0.5)	0.623
Clinically significant bleeding	26	(2)	7	(3)	0.360	2	(1)	5	(3)	0.449
Anemia	51	(5)	10	(5)	0.845	5	(3)	8	(4)	0.547
Septic shock	10	(1)	3	(1)	0.449	0	(0)	2	(1)	0.499
Atrial fibrillation	306	(27)	109	(52)	**0.001**	93	(50)	97	(52)	0.678
Coronary artery disease, n (%)										
Coronary angiography, overall	810	(71)	126	(60)	**0.002**	125	(67)	114	(61)	0.234
Coronary artery disease	593	(73)	105	(83)	**0.015**	96	(77)	94	(40)	0.279
PCI	358	(44)	42	(33)	**0.022**	42	(34)	36	(32)	0.739
Left ventricular ejection function, n (%)										
LVEF ≥ 55%	300	(31)	17	(9)		23	(12)	17	(9)	
LVEF 54–35%	361	(38)	54	(29)	**0.001**	51	(27)	54	(19)	0.111
LVEF < 35%	310	(32)	115	(62)		112	(60)	115	(62)	
Not documented	173	–	24	–		–	–	–	–	–
Cardiac therapies at index, n (%)										
Cardiopulmonary resuscitation	370	(32)	42	(20)	**0.001**	36	(19)	36	(19)	1.000
In hospital	125	(11)	20	(10)	0.546	21	(11)	20	(11)	0.869
Out of hospital	245	(21)	22	(11)	**0.001**	15	(8)	16	(9)	0.851
Electrophysiological examination	385	(66)	155	(74)	**0.034**	48	(26)	74	(40)	**0.004**
VT ablation therapy	70	(6)	25	(12)	**0.003**	21	(11)	13	(7)	0.150
Overall ICDs, n (%)	588	(51)	151	(72)	**0.001**	135	(73)	140	(75)	0.555
Type of ICD, n (%)										
ICD	525	(46)	127	(61)	**0.001**	116	(62)	117	(63)	0.915
s-ICD	20	(2)	3	(1)	0.742	6	(3)	2	(1)	0.153
CRT-D	43	(4)	21	(10)	**0.001**	13	(7)	21	(11)	0.150
ICD implant indication, n (%)										
Primary prevention	257	(44)	63	(42)	0.660	68	(50)	61	(44)	0.259
Secondary prevention	331	(56)	88	(58)		67	(50)	79	(56)	
Medication at discharge, n (%)										
ACE-inhibitor	782	(68)	151	(72)	0.315	141	(76)	130	(70)	0.200
ARB	135	(12)	20	(10)	0.345	26	(14)	19	(10)	0.274
Aldosteron-antagonist	120	(11)	40	(19)	**0.001**	27	(15)	38	(20)	0.133
ASA only	307	(27)	59	(28)	0.711	60	(32)	50	(27)	0.256
Thienopyridine only	28	(2)	9	(4)	0.134	5	(3)	8	(4)	0.397
Dual antiplatelet therapy	389	(34)	48	(23)	**0.001**	46	(25)	42	(23)	0.626
Primary endpoint										
All cause-mortality at 3 years, n (%)	186	(16)	57	(27)	**0.001**	33	(18)	48	(26)	0.060
Follow up data, n (%)										
Hospitalization time (median, (IQR))	12 (7–22)		14 (9–25)		**0.021**	12 (8–25)		15 (9–25)		0.147
ICU time (median, (IQR))	3 (0–7)		4 (0–9)		0.158	2 (0–6)		3 (0–9)		0.212
Follow-up time, days, (mean; median (range))	2020; 1847 (3–5106)		1455; 1293 (15–4786)		**0.001**	2148; 2069 (20–5007)		1445; 1293 (15–4786)		**0.001**

ACE; angiotensin converting enzyme; ARB, angiotensin receptor blocker; ASA; acetyl salicylic acid; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy plus defibrillator; (s-) ICD, (subcutaneous) implantable cardioverter- defibrillator; ICU, invasive care unit; IQR, interquartile range; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; STEMI, ST segment elevation myocardial infarction. Bold type indicates $p < 0.05$.

per day) and bisoprolol (mean dosage 5–6 mg per day). AMIO was taken at mean dosages of 200 mg per day after individual in-hospital loading regimen (Supplemental Table 1). Within BB-AMIO group, AMIO therapy was evidently discontinued in 30 patients (14%) at 3 years of follow up, in these patients, most documented reason for AMIO discontinuation was QTc prolongation (23%) (Supplemental Table 2).

Focusing on the intention-to-treat analysis, patients with BB-AMIO were more likely to be older and of male gender and to have a prior history of arterial hypertension, diabetes, chronic heart failure, CAD and chronic kidney disease. At index stay, AMI and STEMI respectively were more frequent in BB, whereas AF was more common in BB-AMIO (Table 1, left panel).

A higher prevalence of LVEF ≥ 55% was observed in BB, whereas LVEF < 35% was more prevalent in BB-AMIO. BB patients were discharged earlier (median 12 days vs. 14 days), whereas times of ICU treatment were comparable in both groups.

3.2. Survival data in the unmatched cohorts

Median follow up time was 4.8 years (IQR 2.0–8.3 years). Within the unmatched cohort, BB therapy was associated with improved survival compared to BB-AMIO at 3 years of follow-up already (mortality rates 16% versus 27%; log rank $p = 0.001$; HR = 0.550; 95% CI = 0.409–0.740; p = 0.001) (Fig. 1, left panel).

Within the unmatched cohort multivariable Cox regression analyses revealed, that BB was still associated with improved survival over BB-AMIO (HR = 0.712; 95% CI = 0.505–1.003; statistical trend $p = 0.052$) (Table 2A, right panel). Besides BB therapy, an activated ICD was of prognostic benefit (HR = 0.545; p = 0.001).

After applying multivariable Cox regression models within the unmatched subgroups, BB was still associated with improved survival in patients with LVEF ≥35% (HR = 0.477; 95% CI = 0.279–0.814; $p = 0.007$) and in non-AF patients (HR = 0.585; 95% CI = 0.360–0.952; $p = 0.031$) (Table 2B, right panel). Moreover, BB therapy was superior to BB-AMIO in patients who underwent VT ablation therapy during index hospitalization (HR = 0.108; 95% CI 0.021–0.550; p = 0.007).

No mortality differences between BB and BB-AMIO therapy were observed in the presence (HR = 0.749; $p = 0.230$) or absence (HR = 0.699; $p = 0.202$) of an ICD, irrespective of device type (i.e. (s-)ICD only or CRT-D) and implant indication (primary or secondary prevention).

3.3. Propensity-matched study cohort

After applying propensity-score matching for harmonization, a total of 186 matched pairs (50% BB, 50% BB-AMIO) were found (Table 1, right panel). BB-AMIO patients were still older compared to BB patients (median 69 vs. 65 years) and most patients were of male gender. Cardiovascular risk factors and acute and chronic comorbidities were equally distributed within the matched cohort, except for a higher rate of diabetes within the BB-AMIO group. Especially the degree of left ventricular dysfunction, the rate of CPR and the presence and extent of CAD were comparable.

After propensity-score matching, prognostic superiority of BB was still evident (mortality rates 18% versus 26%; log rank $p = 0.042$; HR = 0.634; 95% CI = 0.407–0.988; $p = 0.044$) (Fig. 1, right panel). Sub-group analyses within the matched cohort revealed adverse prognosis for BB-AMIO in patients with LVEF ≥ 35% (mortality rates 14% versus 27%; log rank p = 0.044; HR = 0.463; 95% CI = 0.215–0.997; $p = 0.049$) (Fig. 2A, left panel), whereas in patients with LVEF < 35% no prognostic difference between BB and BB-AMIO was observed (log rank $p = 0.324$) (Fig. 2A, right panel). Accordingly, BB was associated with improved survival within non-AF patients (mortality rates 12% versus 26%; log rank $p = 0.013$; HR = 0.415; 95% CI = 0.202–0.852; $p = 0.017$) (Fig. 2B, right panel), whereas no difference was seen in AF patients (log rank $p = 0.652$) (Fig. 2B, left panel).

3.4. As-treated analysis

Finally, the impact of BB versus BB-AMIO was re-evaluated after excluding patients with evidently discontinued AMIO therapy, since 30 patients discontinued AMIO treatment at 3 years of follow up. Here BB therapy was still associated with improved long-term survival over BB-AMIO before (HR = 0.491; 95% CI 0.362–0.666; $p = 0.001$) and after propensity-score matching (HR = 0.590; 95% CI 0.378–0.921; $p = 0.020$) (Supplemental Fig. 1; left and right panel).

4. Discussion

The present study comparatively evaluates the prognostic impact of BB compared to BB-AMIO therapy on long-term all-cause mortality in patients surviving index episodes of ventricular tachyarrhythmias.

This real-world data suggests that BB therapy is superior compared to combined BB-AMIO, being associated with significantly lower long-

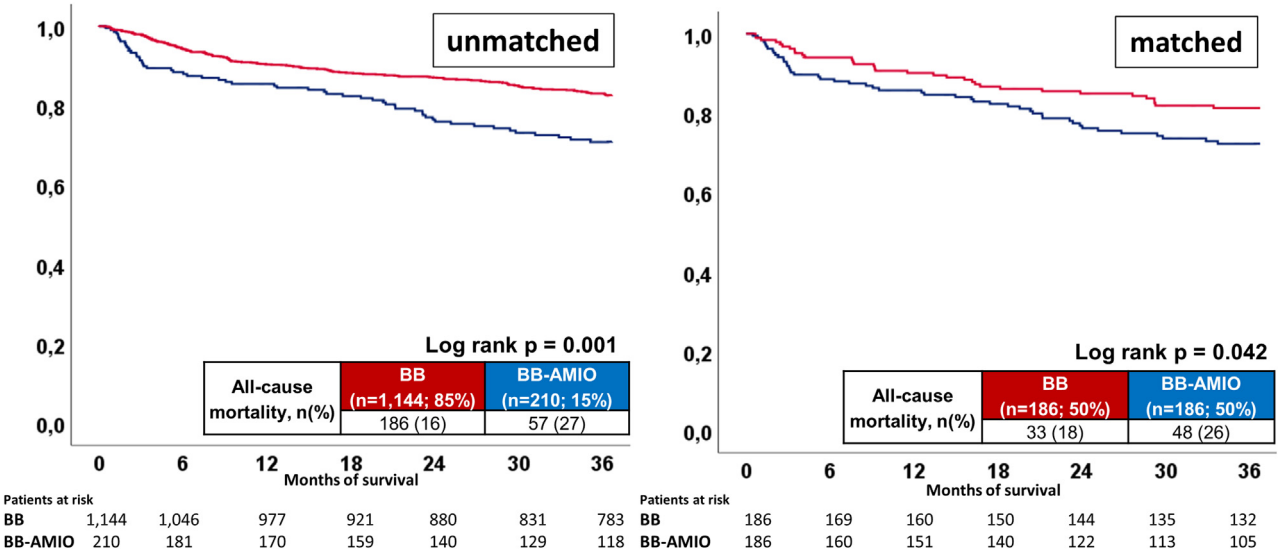

Fig. 1. Overall survival curves comparing BB versus BB-AMIO therapy within the unmatched (left panel) and propensity-matched cohort (right panel).

Table 2A
Uni- and multivariable Cox regression analyses for long-term all-cause mortality within the unmatched cohort (n = 1354).

	Univariable			Multivariable		
	HR	95% CI	*p* Value	HR	95% CI	p Value
Age	1.715	1.506–1.953	**0.001**	1.557	1.336–1.816	**0.001**
Male gender	1.124	0.835–1.512	0.440	1.241	0.789–1.752	0.219
Diabetes	2.167	1.676–2.802	**0.001**	1.655	1.235–2.219	**0.001**
CKD	2.257	1.747–2.915	**0.001**	1.747	1.309–2.333	**0.001**
AF	1.859	1.441–2.398	**0.001**	1.394	1.044–1.861	**0.024**
VF	0.847	0.642–1.118	0.242	0.672	0.449–1.006	0.054
LVEF < 55%	1.992	1.377–2.881	**0.001**	1.763	1.190–2.613	**0.005**
CPR	1.140	0.953–1.363	0.151	1.280	0.992–1.652	0.058
ICD only	0.757	0.621–0.921	**0.005**	0.545	0.401–0.740	**0.001**
CRT-D	0.968	0.725–1.291	0.823	1.266	0.869–1.845	0.219
Ablation therapy	0.533	0.312–0.911	**0.021**	0.694	0.352–1.367	0.290
BB (vs. BB-AMIO)	0.550	0.409–0.740	**0.001**	0.712	0.505–1.003	0.052

AF, atrial fibrillation; CRT-D, cardiac resynchronization therapy plus defibrillator; CI; confidence interval; CKD, chronic kidney disease; CPR, cardiopulmonary resuscitation; HR; hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection faction; VF, ventricular fibrillation. Bold type indicates p < 0.05.
Level of significance p < 0.05, statistical trend *p* < 0.1.

term all-cause mortality at 3 years of follow-up both within unmatched and matched study cohorts. The prognostic benefit of BB was evident especially in patients with LVEF ≥ 35% and non-AF patients, even after multivariable adjustment for age, gender, diabetes, CPR, CKD, AF, presence of an ICD, CRT-D, ablation therapy and LV dysfunction.

Beside treatment with an ICD, treatment and prevention of ventricular tachyarrhythmias relies on suppression of arrhythmogenesis by antiarrhythmic drugs, heart failure treatment to improve LV dysfunction, heart failure devices and on coronary revascularization by PCI or CABG. European guidelines recommend BB to treat and prevent ventricular tachyarrhythmias (class of recommendation I, level of evidence A) [9]. BB were shown to reduce SCD rates and mortality in post-AMI patients and in patients suffering from heart failure. A survival benefit in patients with chronic heart failure was shown in the CIBIS-II trial due to bisoprolol treatment [26]. In line, improved survival was observed in patients treated with metoprolol in the MERIT-HF trial. [27] However, no study specifically focused on patients presenting with ventricular tachyarrhythmias and the prognostic effect of BB compared to BB-AMIO.

In contrast, guidelines suggest careful use of "classic" antiarrhythmic drugs, such as AMIO to prevent both the onset and recurrences of VT in patients with and without ICD (class of recommendation II, level of evidence C) [9]. Additionally, further studies demonstrated efficacy of AMIO in patients with myocardial infarction and heart failure. A meta-analysis including 6500 post-MI patients and patients with heart failure demonstrated a reduction of arrhythmic and sudden death as well as a decrease of mortality with prophylactic amiodarone therapy [28]. The EMIAT trial including post-AMI patients with LVEF < 40% revealed a decrease of arrhythmic death, but no differences in cardiac and all-cause mortality [29]. Combined therapy with BB plus AMIO was analyzed within the randomized OPTIC trial only, demonstrating a reduction of ICD shocks due to BB-AMIO in 94 patients with an activated ICD [19].

Moreover AMIO is the only antiarrhythmic drug, which can be applied in patients with systolic heart failure, whereas available data in this setting are conflicting. For instance, the SCD-HeFT trial compared amiodarone to ICD treatment in patients with NYHA II and NYHA III class and LVEF < 35% and proved no survival benefit in patients treated with AMIO [30]. The present study might support this evidence, since no differences in prognosis were seen in patients with LVEF < 35% neither for BB nor BB-AMIO therapy. Accordingly, the presence of an activated ICD balanced the adverse prognostic effect of BB-AMIO. The adverse prognostic effect of BB-AMIO might be explained by AMIO and its multiple side effects on thyroid, lungs and liver [9]. Increased non-cardiac and all-cause mortality due to anti-arrhythmic treatment was observed in a meta-analysis including 15 trials with 18,000 patients [31]. In our study, discontinuation of AMIO treatment due to its side effects was necessary in 15% in BB-AMIO group. In order to replace AMIO due to its side effects, multiple studies compared AMIO to ICD therapy alone. Analyses based on the entire real-life cohort in this study demonstrated an adverse prognostic effect of BB-AMIO despite the presence of an ICD.

Besides AMIO therapy, reduction of recurrent ventricular tachyarrhythmias and associated ICD therapy may also be achieved by interventional ablation therapy [32]. Here, catheter ablation was shown to reduce ICD therapies in a RCT including 64 patients with ICD and 64 patients with ICD plus ablation after MI [33]. VT ablation therapy was shown to be effective in many cases with success rates of 44% after single and 60% after multiple ablations [34]. Comparing VT ablation therapy to AMIO only, both strategies were shown to significantly and comparably reduce the risk of recurrent VT episodes, whereas a trend

Table 2B
HRs with 95% CIs for BB vs. BB-AMIO within the specific unmatched subgroups.

	Univariable				Multivariable*		
	N (%)	HR	95% CI	p Value	HR	95% CI	p Value
Overall	1354 (100)	0.550	0.409–0.740	**0.001**	0.712	0.505–1.003	0.052
Females	342 (25)	0.522	0.247–1.103	0.088	–	–	–
Males	1012 (75)	0.561	0.405–0.778	**0.001**	0.724	0.499–1.051	0.090
VT	917 (68)	0.563	0.400–0.792	**0.001**	0.750	0.508–1.108	0.149
VF	437 (32)	0.537	0.294–0.981	**0.043**	0.687	0.329–1.436	0.318
LVEF ≥ 35%	732 (54)	0.391	0.236–0.645	**0.001**	0.477	0.279–0.814	**0.007**
LVEF < 35%	425 (31)	0.911	0.594–1.399	0.671	–	–	–
ICD only	675 (50)	0.593	0.388–0.907	**0.016**	0.749	0.467–1.200	0.230
Primary prevention	282 (21)	0.527	0.258–1.079	0.080	0.628	0.290–1.362	0.239
Secondary prevention	393 (29)	0.646	0.381–1.095	0.105	–	–	–
Preexisting ICD	207 (15)	0.689	0.415–1.143	0.149	–	–	–
CRT-D	64 (5)	0.656	0.208–2.068	0.472	–	–	–
Non-ICD	615 (45)	0.445	0.285–0.694	**0.001**	0.699	0.404–1.211	0.202
AF	415 (31)	0.819	0.536–1.253	0.358	–	–	–
Non-AF	939 (69)	0.474	0.312–0.722	**0.001**	0.585	0.360–0.952	**0.031**
Ablation therapy	95 (7)	0.215	0.075–0.621	**0.005**	0.108	0.021–0.550	**0.007**
No ablation therapy	1259 (93)	0.595	0.434–0.815	**0.001**	0.791	0.551–1.136	0.204

AF, atrial fibrillation; CI; confidence interval; CRT-D, cardiac resynchronization therapy plus defibrillator; HR; hazard ratio; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection faction; VF, ventricular fibrillation; VT, ventricular tachycardia. Bold type indicates p < 0.05.
Level of significance p < 0.05; statistical trend p < 0.1.

* Multivariable models were adjusted for age, gender, diabetes mellitus, chronic kidney disease, type of ventricular tachyarrhythmia (VT or VF), LV dysfunction, cardiopulmonary resuscitation and presence of an activated (s-)ICD or CRT-D.

of increased mortality was shown in patients treated with AMIO [35]. However, there is still heterogeneity regarding current healthcare supply in European countries in the management of ablation therapy for VT patients, although it represents the first-line therapy especially in patients with recurrent, stable monomorphic VTs [36]. Our study demonstrates decreasing all-cause mortality in patients with BB compared to BB-AMIO after undergoing VT ablation therapy. Therefore the present study supports current trends indicating increased mortality in patients with AMIO therapy and in those with escalated anti-arrhythmic drug therapies [37,38]. However, the subgroup of patients undergoing VT ablation was small in our study (95 patients).

The prognostic impact of AMIO was compared to an activated ICD in 659 patients with sustained VT or VF within the CIDS study, demonstrating a reduction of all-cause mortality of 20% and a 33% reduction of arrhythmic mortality due to ICD therapy [39]. The impact of ICD therapy has also been demonstrated in the MADIT-II trial including 1232 post-MI patients with LVEF ≤ 30% [40]. In our study, BB and BB-AMIO therapy were associated with comparable mortality across all ICD subgroups (i.e. ICD only, CRT-D, primary and secondary preventive ICD).

In conclusion, this study demonstrates that treatment with BB improves long-term prognosis in patients surviving ventricular tachyarrhythmias, whereas BB-AMIO was associated with impaired mortality. Long-term treatment with AMIO should be recommended with caution especially in patients presenting with LVEF ≥ 35% and those without AF. Whether ablation therapy of ventricular tachyarrhythmias might improve survival, especially in patients without LVEF < 35% and VT only counterbalancing the adverse effect of BB-AMIO is beyond the scope of the present study. This is due to low ablation rates in both BB and BB-AMIO patients and need to be evaluated in future randomized controlled studies.

5. Study limitations

This observational and retrospective registry-based analysis reflects a realistic picture of consecutive health-care supply of high-risk patients presenting with ventricular tachyarrhythmias. Lost to follow-up rate regarding the evaluated endpoint of all-cause mortality was minimal. Risk stratification was performed according to pharmacological therapies focussing on discharge medication at index event (intention-to-treat

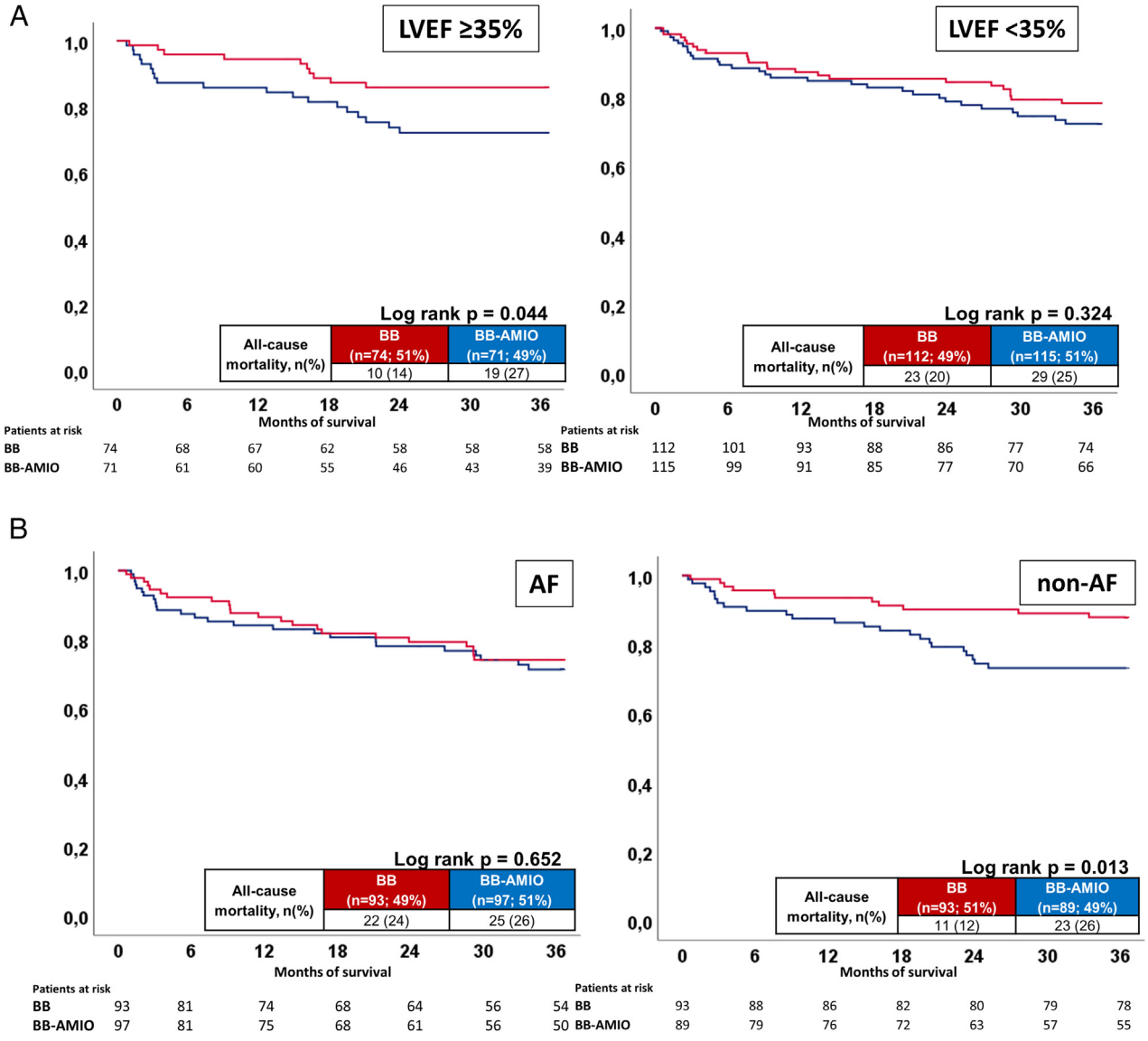

Fig. 2. A: Survival curves comparing BB versus BB-AMIO therapy within the matched subgroups of LVEF ≥ 35% (left panel) and LVEF < 35 (right panel). **B:** Survival curves comparing BB versus BB-AMIO therapy within the matched subgroups of AF (left panel) and non-AF patients (right panel).

analysis). To reduce a potential selection bias due to discontinuous AMIO treatment, the impact of BB versus BB-AMIO was finally re-evaluated after excluding patients with discontinued AMIO treatment (as-treated analysis). Beyond selection bias may also not be excluded for instance in patients not surviving out of hospital CPR while not being transferred to our clinic, which were not included in the present study. Additionally, heterogeneity within the study population was controlled by a stepwise statistical approach including multivariable adjustment for several important comorbidities and risk factors, within the entire cohort and specific unmatched subgroups. However, even after applying propensity score matching some cofounding may still be present because BB-AMIO patients were still older within the matched cohort. Sub-analyses within the multivariable cox regression models regarding the subgroup of patients undergoing VT ablation therapy, as well as sub-analyses in the propensity-matched cohorts (i.e. non-AF and LVEF < 35% groups) might be influenced by a relatively low rate of events, especially in BB-patients. All clinical data was documented reliably by individual cardiologists during routine clinical care being blinded to final analyses, alleviating the use of an independent clinical event committee. The present results need to be re-evaluated within even larger and more representative multi-centre registry data or even randomized controlled trials, especially focusing on the impact of BB-AMIO in selected subgroups with additional ablation therapy.

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Conflict of interest

The authors declare that they do not have any conflict of interest.

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